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EXAMINER	
CANELLA, KAREN A	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 07/07/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/897,724	LE ET AL.	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *5-7 and 13* is/are allowed.

6)☐ Claim(s) *1-4,8-12 and 14-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/16/02+10/15/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-18 are pending and examined on the merits.

Acknowledgment is made to applicants claim to an earlier effective filing date via 08/010,406, filed Jan 29, 1993; 08/013,413, filed February 2, 1993; 07/943,852, filed September 11, 1992; 07/853,606, filed March 18, 1992; 07/670,827, filed March 18, 1991. Upon review of each of these documents it is noted that only 08/010,406 contemplates anti-idiotypic antibodies to TNF; none of the prior applications contemplates anti-anti-idiotypic antibodies to TNF. Thus, none of the prior applications provides adequate written description for an anti-anti-idiotypic antibody to TNF and only the 08/010,406 application provides an adequate written description of an anti-idiotypic antibody to TNF. Accordingly claims 1-13 and 17 are given the effective priority date of Jan 29, 1993 commensurate with the '406 application. Claim 14-16 and 18, drawn to anti-anti-idiotypic antibodies will be given the effective date of July 2, 2001 commensurate with the instant filing date.

It is noted that the specification defines the cA2 antibody as comprising the variable domains of SEQ ID NO:3 and 5 fused to the IgG1 kappa domain as stated on page 12, lines 19-24 and page 36, lines 18-21 of the specification..

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3, 8-12, 17 and 18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites "an anti-idiotypic antibody...that binds specifically to a chimeric or humanized antibody". Claim 10 also recites the limitations of "chimeric" or "humanized" antibody. It is unclear how the limitation of "chimeric or humanized" serves to limit the anti-

idiotypic antibodies claimed, because said anti-idiotypic antibodies will bind to the idiotype of the chimeric or humanized antibody and not to the isotype. Thus, the limitation of binding to a chimeric or humanized antibody does not set apart an anti-idiotypic antibody from anti-idiotypic antibodies which bind to the non-chimeric or non-humanized antibody because the antibody, chimeric antibody and humanized antibody will all have the same idiotype. For purpose of examination, the limitation of chimerized or humanized will not be considered as limiting the claimed anti-idiotypic antibody.

Claim 2 recites "an epitope specific for human TNF-alpha". It is unclear how this "specificity" eliminated other antibodies from the metes and bound of the claims. It is noted that the specification teaches that the cA2 antibody binds both to chimpanzee and human TNF (page 87, lines 28-35). Thus, the specification allows for some binding to TNF from other species within the limitation of "specific" binding to human TNF-alpha. However, the specification does not provide a definition of "specific" in the context of binding to human TNF-alpha that would definitely set the metes and bounds of the claim.

It is unclear how claim 8 further limits claim 5. Claim 8 recites an anti-idiotypic antibody which comprises SEQ ID NO:3 or 5. However, these sequence are part of the cA2 antibody and would not be part of an antibody which would bind to the idiotype of the cA2 antibody.

It is unclear how claim 9 differs in scope from claim 5. Claim 9 recites that the anti-idiotypic antibody must contain an antigen binding site specific for cA2. This property would be inherent in the anti-idiotypic antibody of claim 5.

The antecedent basis of "antibody" in section b of claims 17 and 18 is unclear as both claims recite two different antibodies in section a of the method. Further, it is unclear if the "antibody to an antibody" as recited in claim 17 and the "antibody to an anti-idiotypic antibody" as recited in claim 18 encompass antibodies which bind to the antibody and antiidiotypic antibody isotype in addition to the idiotype. For purpose of examination, both alternatives will be considered.

Claim 17 lacks a method step which relates the binding to the antibody to TNF with the method objective of detecting an anti-TNF antibody in a sample.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 8 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 8 is drawn to an anti-idiotypic antibody which is specific for cA2 and which comprises an amino acid sequence selected from the group consisting of SEQ ID NO:3 and 5. The specification teaches that cA2 comprises the variable chains of SEQ ID NO:3 and SEQ ID NO:5. An antibody which specifically binds the idiotype of cA2 would not contain the amino acid sequence of said idiotype.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2 and 12 are rejected under 35 U.S.C. 102(a) as being anticipated by Galloway et al (European Journal of Immunology, Nov. 1992, Vol. 22, pp. 3045-3048) or Barbanti et al (EP 492,448).

Claim 1 is drawn to an anti-idiotypic antibody or functional fragment thereof that specifically binds a chimeric or humanized antibody that bind to human TNF-alpha. For the reasons stated in the rejection under 112, second paragraph above, the limitation of "chimeric or

humanized antibody" does not limit the anti-idiotypic antibody claimed. Claim 2 embodies the anti-idiotypic antibody of claim 1, wherein said anti-idiotypic antibody binds to an anti-TNF antibody at an epitope specific for human TNF-alpha. For the reasons stated in the rejection under 112, second paragraph above, the term "specific" in the context of the antibody which binds to human TNF-alpha does not have defined metes and bounds. Claim 12 is drawn to a kit comprising the anti-idiotypic antibody of claim 1.

Galloway et al disclose an anti-idiotypic antibody which binds to the A10G10 antibody which binds human TNF alpha (page 3045, second column, under "Reagents and Cell lines" and "Rabbit Immunizations").

Barbanti et al teach a monoclonal anti-idiotypic antibody which binds to the human TNF-alpha receptor (claim 17). An anti-idiotypic antibody which binds to the human TNF receptor would also bind the antibody which specifically binds human TNF as evidenced by Rathjen et al (WO 93/01211) who teach that anti-idiotypic antibodies to a peptide hormone can function like the peptide hormone and interact specifically with receptors for said peptide hormone (page 13, lines 1-7).

It is noted that claim 12 drawn to a kit does not comprise a limitation other than the anti-idiotypic antibody. Thus the disclosure of an anti-idiotypic antibody fulfills the specific embodiments of claim 12.

Claim 17 is rejected under 35 U.S.C. 102(b) as being anticipated by Moller et al (Cytokine, 1990, Vol. 2, pp. 162-169, reference of the IDS filed September 16, 2002).

Claim 17 is drawn to an immunoassay method for detecting anti-TNF-antibody in a sample comprising contacting said sample with an antibody to an antibody comprising an amino acid sequence selected from the group consisting of SEQ ID NO:3 or 5, or a TNF binding fragment thereof, in detectably labeled form, and detecting the binding of the antibody to TNF.

Moller et al disclose a method wherein horseradish peroxidase conjugated anti-mouse IgG is reacted with a sample comprising anti-TNF antibodies bound to TNF-alpha. The anti-mouse IgG fulfills the specific embodiment of an antibody to an antibody comprising an amino acid sequence selected from the group consisting of SEQ ID NO:3 and 5 because the claim does not state that the antibody must be an anti-idiotypic antibody versus and anti-isotypic antibody.

It would be expected that the anti-mouse IgG would bind to the A2 antibody comprising SEQ ID NO:3 and 5. Further, the claim lacks a specific method step for linking the antibody comprising SEQ ID NO:3 or 5 to fulfill the method objective of detecting an anti-TNF antibody.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 4, 11 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barbanti et al (EP 492,448) in view of Moller et al (Cytokine, 1990, Vol. 2, pp. 162-169)..

The specific embodiments of claims 1, 2 and 12 are recited above. Claim 4 embodies an anti-idiotypic antibody or functional fragment thereof that binds an anti-TNF antibody , wherein said anti-TNF antibody competitively inhibits binding of cA2 to human TNF-alpha. Claim 11 is drawn to a hybridoma producing an anti-idiotypic antibody of claim 1.

Barbanti et al (EP 492,448) teach an anti-idiotypic antibody to anti human TNF antibody which binds to the human TNF-alpha receptor. Barbanti et al do not teach anti-idiotypic antibodies which bind to antibodies which competitively inhibit the binding of cA2 to human TNF-alpha.

Moller et al teach the mAb195 which specifically binds TNF from humans and chimpanzees, but which does not bind to mouse, rat, rabbit, dog or pig TNF (Table 2). The instant specification describes A2 as binding to human and chimpanzee TNF but not binding to mouse, rat, rabbit, dog or pig TNFalpha (page 87, lines 28-35). Thus, it appears that the instant A2 and chimerized A2 bind to the same or a overlapping epitope as mAb195, and therefore would compete for binding to TNF with A2 and cA2. Moller et al teach that mAb195 can bind to TNF alpha when TNF alpha was bound to the TNF receptor and that this suggests an alternative mechanism for the neutralization of the biological activity of TNF-alpha by the mAb195 antibody which does not involve the blocking of the binding of TNF alpha to its receptor. Moller et al discriminates between receptor binding epitopes of TNF alpha and neutralization epitopes of TNF alpha (page 166, first column, lines 13-22). Moller et al do not teach an anti-idiotypic antibody to mAb195.

It would have been prima facie obvious at the time he invention was made to make the anti-idiotypic antibody of mAb195. One of skill in the art would have been motivated to do so by the teachings of Moller et al in order to obtain an antibody which would react with the ligand which bound the TNF neutralizing epitope of TNF rather than the receptor binding epitope of TNF. One of skill in the art would have been motivated to identify proteins which interacted with TNF and elaborated the toxic activity of TNF in order to identify proteins for therapeutic intervention in TNF-mediated pathologies.

Claims 14 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Moller et al (Cytokine, 1990, Vol. 2, pp. 162-169) in view of Lee et al (WO 92/12176).

Claim 14 is drawn to an anti-anti-idiotypic antibody having the identical binding specificity to an anti-TNF alpha antibody comprising at least a part of a non-human immunoglobulin variable region, said anti-TNF alpha antibody capable of binding an epitope specific for human TNF alpha. Claim 18 is drawn to an immunoassay method for detecting human TNF in a sample comprising contacting said sample with an antibody to an anti-idiotypic antibody of claim 1, or a TNF binding fragment thereof in a detectably labeled form; and detecting the binding of the antibody to said TNF alpha.

Moller et al teach the mAb195 which specifically binds TNF from humans and chimpanzees, but which does not bind to mouse, rat, rabbit, dog or pig TNF (Table 2). The instant specification describes A2 as binding to human and chimpanzee TNF but not binding to XY ad Z TNF. Thus, it appears that the instant A2 and chimerized A2 bind to the same or a overlapping epitope as mAb195, and therefore would compete for binding to TNF with A2 and cA2. Moller et al teach that mAb195 can bind to TNF alpha when TNF alpha was bound to the TNF receptor and that this suggests an alternative mechanism for the neutralization of the biological activity of TNF-alpha by the mAb195 antibody which does not involve the blocking of the binding of TNF alpha to its receptor. Moller et al discriminates between receptor binding epitopes of TNF alpha and neutralization epitopes of TNF alpha (page 166, first column, lines 13-22). Moller et al teach an immunoassay wherein human TNF alpha is quantified using the mAb195 antibody which specifically binds human TNF alpha (page 164, second column, under the heading "Quantification of TNFa Using an ELISA Method"). Moller et al do not teach an anti-anti-id antibody which would bind to human TNF-alpha.

Lee et al (WO 92/12176) teach that an anti-id antibody is an antibody which recognizes unique determinants associated with the antigen binding site of an antibody. Lee et al teach that the anti-id antibody may be used as an immunogen to induce an immune response in a host animal and produce an anti-anti-id antibody which would bear structural resemblance to the original mAb which induced the anti-id (page 41, lines 9-23). Lee et al teach that by using antibodies to the idiotypic determinants of mAb it is possible to identify other clones expressing antibodies of identical specificity.

It would have been prima facie obvious at the time the invention was made to make anti-anti-id antibodies which bound to TNF alpha by using the mAb195, and to substitute said anti-anti-id antibodies for the mAb195 antibody in an immunoassay for TNF-alpha. One of skill in the art would have been motivated to do so by the teachings of Lee et al on the identification of other clones of antibodies expressing the identical specificity of the original antibody by means of making the anti-anti-id antibody to the original antibody.

Claims 14-16 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Le et al (WO 92/16553, reference of the IDS filed September 16, 2002) in view of Lee et al (WO 92/12176).

Claim 14 is drawn to an anti-anti-idiotypic antibody having the identical binding specificity to an anti-TNFalpha anybody comprising at least part of a non-human immunoglobulin variable region, said anti-TNFalpha antibody capable of binding an epitope specific for human TNFalpha. Claim 16 is drawn to an anti-anti-idiotypic antibody having the identical binding specificity to an anti-TNFalpha antibody , wherein said anti-TNFalpha antibody has a non-human immunoglobulin variable domain encoded by SEQ ID NO:2 or SEQ ID NO:4.

The specification teaches that the A2 antibody has non-human immunoglobulin variable domains encoded by SEQ ID NO:2 and 4.

Le et al teach the monoclonal antibody of A2 which is a murine antibody specific for human TNFalpha.

Lee et al (WO 92/12176) teach that an anti-id antibody is an antibody which recognizes unique determinants associated with the antigen binding site of an antibody. Lee et al teach that the anti-id antibody may be used as an immunogen to induce an immune response in a host animal and produce an anti-anti-id antibody which would bear structural resemblance to the original mAb which induced the anti-id (page 41, lines 9-23). Lee et al teach that by using antibodies to the idiotypic determinants of mAb it is possible to identify other clones expressing antibodies of identical specificity.

It would have been prima facie obvious at the time the claimed invention was made to make anti-anti-idiotypic antibodies to human TNFalpha by making an antibody to an anti-idiotypic antibody of A2. One of skill in the art would have been motivated to do so by the teachings of Lee et al on the identification of other antibodies of the same specificity which bind to an antigen by making anti-anti-id antibodies.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10 a.m. to 9 p.m. M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571)272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.
6/28/2004

KAREN A. CANELLA PH.D
PRIMARY EXAMINER